Pharmacotypes within the schizophrenias

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I love drugs!

• They can alleviate symptoms, ease suffering, sometimes even eradicate diseases.

• They tell the truth

• In a field like psychiatry, where illness are often described by fuzzy concepts or psychic experiences,
  – Drugs are touchstones to physiological reality

• If a symptom/illness improves in response to a medication, then the target(s) of that medication may be relevant to the cause of the illness

• If a symptom/illness does not respond to a medication, then that medication’s target(s) may not be relevant to illness expression.
Medications can inform about pathophysiology

- Agents of therapy

- Interrogators of physiology
  - Every treatment is an implicit test of a pathophysiological hypothesis
  - Variable patterns of medication response may imply a variety of underlying disease processes
Imagine ‘Cough, Dyspnea and High Body Temperature Disorder’ **CDHD**

- **Criterion A:** Elevated temperature and Cough
- **Criterion B:** Duration > 3 days
- **Criterion C:** Accompanied by at least two of the following: malaise, myalgia, decreased appetite, chills, diminished interest in formerly pleasurable activities, sweating
- **Criterion D:** Symptoms are not better explained by a different diagnosis

70% of patients with CDHD achieve rapid remission with penicillin (first-generation, or *typical* antipyretic agent)

**Conclusion:** CDHD is caused by gram-positive bacteria
Treatment-resistant CDHD, Scenario 1

• Treatment-resistant CDHD represents about 30% of CDHD cases
• 10% to 15% of those cases will respond favorably to second-generation, or atypical antipyrotussive agents (e.g. ceftriaxone)

• Long-acting injectable agents (penicillin or ceftriaxone) can be effective when medication adherence is sporadic.

• Sporadic literature reports and pockets of accepted practice for TR-CDHD may include:
  – Combining oral agents with injectable agents
  – Multiple agents (penicillin, amoxicillin, cephalexin polypharmacy)
  – High-dose agents (2- to 3-fold above standard doses of penicillin)
Simple Example, Scenario 2

- 70% of CDHD cases are caused by gram positive bacteria.
- Non-response to standard agents (penicillin), assuming adequate dosing, suggest that symptoms arise from some other cause.
- Next step in treatment will target some other pathway.

<table>
<thead>
<tr>
<th>Pharmacotype A</th>
<th>PCN-sensitive</th>
<th>Gram-positive infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacotype B</td>
<td>Azithromycin-sensitive</td>
<td>Gram-negative infection</td>
</tr>
<tr>
<td>Pharmacotype C</td>
<td>Isoniazid-sensitive</td>
<td>Mycobacterial infection</td>
</tr>
</tbody>
</table>
Pharmacotypes are abundant in medicine

Hypertension

• Fabulously relevant example when talking of psychiatric illness
• Easy to detect, seemingly simple to understand, but with many causes and variable medication response

• Reduce intravascular volume
• Reduce arterial tone
  – Nitrates
  – Calcium channel blockers
  – Oppose angiotensin
• Reduce force of heart contraction

 Preferential response to one type of anti-HTN agent points to the relevance of that agent’s target in the cause of an individual’s hypertension
Schizophrenia as a heterogeneous group of disorders

• Original description was of a group of multiple illnesses: “the group of schizophrenias”
• “for the sake of convenience, I use the word in the singular, although it is apparent that the group includes several diseases” (Bleuler, 1920)

Conceptual pedigree favors heterogeneity

- Hybrid philosophical nature of the schizophrenia construct
- Blends Kraepelin’s germ-theory-informed notion of an Alzheimer-like persistent degenerative disease (dementia praecox)
- With Bleuler’s Freudian psychodynamics-informed focus on mental processes (the group of schizophrenias)
Divergent clinical course is consistent with different diseases within the schizophrenias

Pre-Pharmacotherapy Era
Eventual Recovery vs Persistent Illness
- 13% of Kraepelin’s dementia praecox patients recovered
- 23% of a 1942/43 schizophrenia patient cohort experienced full recovery; 43% with sustained significant improvement

Modern Era
- 20% of patients with first-episode schizophrenia could maintain remission after medication discontinuation
- 30% could maintain remission with low-dose medications
- 50% required standard dosing
Divergent clinical course is consistent with multiple illnesses within schizophrenia, but is far from conclusive evidence.

If a new behavioral syndrome were recognized in this modern era, how might we study it?
If schizophrenia were discovered today: An agnostic, atheoretical approach based on big data cluster analysis

- 17 independent genetic/biochemical diseases
- 8 distinct clinical syndromes


Genetic clusters

Genetic x Phenotypic Interactions

This material provided by the Best Practices in Schizophrenia Treatment (BeST) Center, Department of Psychiatry, Northeast Ohio Medical University.
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If schizophrenia were discovered today: cluster analysis of quantitative EEG data

6 distinct EEG signatures of prolonged psychosis

- Based on cluster analysis of quantitative EEG studies
- Originally identified in 94 subjects with schizophrenia
- Replicated in 390 subjects with psychosis from schizophrenia, and additional psychosis-associated conditions (depression, alcohol withdrawal)
- EEG subtypes of psychosis are consistent across disease states

If schizophrenia were discovered today:

The classical pharmacology approach
If 'schizophrenia' were discovered today: the classical pharmacology approach

Minimum of 4 distinct PHARMACOTYPES:

Type 1
  Rapid and robust response to D2 receptor (D2R) antagonists
Type 2
  Slow yet robust response to D2R antagonists
Type 3
  No significant response to DR2 antagonists.
  Good response to clozapine
Type 4
  No significant response to D2R antagonists.
  No therapeutic benefit from clozapine
Pharmacotypes within the schizophrenias

<table>
<thead>
<tr>
<th>Type</th>
<th>Time frame</th>
<th>Magnitude</th>
<th>Dopamine</th>
<th>Brain Volume</th>
<th>Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rapid (weeks)</td>
<td>Robust</td>
<td>Elevated</td>
<td>Stable</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Slow (months)</td>
<td>Robust</td>
<td>Normal</td>
<td>Unstable</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>N/A</td>
<td>Minimal</td>
<td>Normal</td>
<td>Stable</td>
<td>No</td>
</tr>
</tbody>
</table>

- Patients with dopamine disease get rapid benefit from dopamine blockers
- Absence of dopamine biomarkers predicts slow- or non-response to non-clozapine antipsychotic medications

*Garver et al., 2003*
Dopamine biomarkers delineate 2 types of illness; and associate with treatment response

**Type A.** Hyper-dopaminergic persistent psychotic disorder (‘treatment responsive’)

**Type B.** Normal-dopamine persistent psychotic disorder (‘treatment resistant’)
Two illnesses based on dopamine metabolite levels

- Lower levels: Treatment resistant
- Higher levels: Treatment responsive

Two illnesses based on dopamine synapse density

- Electron microscopic study, \textit{post mortem}
- Tyrosine hydroxylase (TH) immunoreactivity
- TH is a marker of DA synapses
- Higher density of DA synapses in treatment responders

Two illnesses based on dopamine receptor density

- Two subtypes based on **bimodal** D2 receptor density *post mortem*
- Bimodality is not an artifact of medication use

Two illnesses based on PET scan dopamine synthesis capacity

- Treatment responders had elevated dopamine synthesis in PET Scan protocol
- Non-responders had DA synthesis rates equivalent to control group
- Finding was replicated in 2017 (Kim et al., 2017)
Summary

• Several lines of evidence suggest that there are multiple schizophrenias
• Variable patterns of medication response suggest 4 distinct pharmacotypes within behaviorally-defined schizophrenia
• Biochemical data support Type A (high-dopamine) and Type B (normal-dopamine) psychotic illness
• Aside from clozapine, there are few well-studied non-dopamine-antagonist pharmacotherapies
• This should be a priority area for research